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**UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/978,634	11/25/97	RABBANI	E ENZ-53(DIV-2)

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HM12/0217

EXAMINER

SCHMIDT, M

ART UNIT

PAPER NUMBER

1635

DATE MAILED:

02/17/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/978,1034

Applicant(s)

Rabbani et al.

Examiner

Schmidt

Group Art Unit

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—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☐ Responsive to communication(s) filed on _____.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 2-24 and 245-279 is/are pending in the application.
Of the above claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 2-24 and 245-279 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____.
 - ☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☒ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☒ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

Office Action Summary

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DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures: Sequences in this specification and/or the claims are not referenced by sequence identifiers.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3. Claims 2-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 2-24 of copending Application Nos.: 08/978,632, 08/978,633, 08/978,635, 08/978,636, 08/978,637, 08/978,638, 08/978,639, and 08/574,443. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

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Claim Rejections - 35 USC § 112

4. Claims 2-21, 245-246, 262, and 279 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-21 are indefinite because they depend from canceled claim 1. Therefore, claims 2-21 do not depend on any indefinite claim.

Claim 245 is indefinite for location of a period in the claim after the word "attached."

There is no antecedent basis in claim 246 for the language "the polymer or oligomer."

Claim 262 is drawn to the same element "polycationic interactions or polycationic interactions" and is redundant.

It appears from the language of claim 279 that the word "complex" should be in the past tense.

5. Claims 2-21 and 245-279 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The constructs taught in the claims 2-24 are broadly drawn to a multitude of possible nucleic acid based constructs for use in a cell to produce a product (and in any context, *in vivo* or *in vitro*), comprising: (1) the construct as linear or circular, (2) the construct as comprising 1,2 or

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3 strands, (3) comprising a terminus, a polynucleotide tail which can hybridize, (4) composed of RNA or DNA or combinations, (5) containing chemically modified nucleotides or analogs, (6) containing non-nucleic acid entities composed of polymers or ligands or a combination, (7) further specifying the natural and synthetic polymers, the synthetic homo- or heteropolymer with a net charge, (8) the construct imparting a "further biological activity" by the modified nucleotide, analog, entity, ligand or combination of those, further defined as nuclease resistance, cell recognition, cell binding, and cellular or nuclear localization or a combination, (9) a ligand attached to one of the modified nucleotides, etc. of claim 1, further described as attached to a "segment" or "tail" of the construct, and further defined as being a macromolecule or small molecule or combination. Claims 22-24 describe a second construct "which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand."

Claims 245-266 are drawn to a composition of a multimeric complex of more than one monomeric unit attached: (a) to each other through polymeric interactions, or (b) to a binding matrix through polymeric interactions, or both. Dependent claims are drawn to (1) linear or branched polymer or oligomers, homopolymer or heteropolymer, (2) an analyte-specific moiety, capable of recognizing a component in a biological system, being: a virus, phage, bacterium, cell or cellular material, tissue, organ or organism, or combination, or from a protein (antibody, hormone, growth factor, lymphokine or cytokine and a cellular matrix protein or a combination), polysaccharide, fatty acid, fatty acid ester and a polynucleotide (linear or circular and single

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stranded) or a combination (3) a naturally occurring compound, a modified natural compound, synthetic compound and a recombinantly produced compound, or combination, (4) linear or branched binding matrix selected from a naturally occurring compound, a modified natural compound, a synthetic compound and a recombinantly produced compound or a combination, also selected from a polypeptide, a polynucleotide and a polysaccharide, or a combination, (5) polymeric interactions selected from ionic, H-bonding, dipole-dipole, or a combination, (6) an entity attached to the binding matrix, being a ligand or compound which increases the binding of the binding matrix.

Claims 275-279 are further drawn to a multimeric composition having more than one unit attached to a charged polymer selected from: a polycationic polymer, a polyionic polymer, a polynucleotide, a modified polynucleotide and analog, or a combination. The composition is further limited to a protein component being an antibody or the F(ab')₂ fragment, where the antibody is further completed with a target comprising an enzyme.

Claims 267-274 are drawn to a process for delivering a cell effector to a cell comprising providing the multimeric complex of claim 245 (where the multimeric unit is the cell effector) and administration (claims 267-270) and a process for delivering a gene or gene fragment to a cell comprising providing the multimeric complex of claim 245 (where the multimeric unit is the gene or fragment) and administration.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic

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acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

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Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A, B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the “A” antisense T7 operon , the “B” antisense T7 operon and the “C” antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs (“various U1 constructs described above” p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the “U1 clone” (p. 169, line 3), (2) expression of the “triple U1

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construct” (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Claims 22-24 read on any construct bound non-ionically to a ligand or otherwise chemically modified entity, further limited as having a polynucleotide tail terminus and where the tail is hybridized to a complementary polynucleotide sequence. The breadth of genus sought for such is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims vaguely claim “constructs” which “produce products.” The specification teaches only by way of example HIV

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inhibition by antisense expression from vector constructs which do not entail chemical modified entities nor polynucleotide termini.

Claims 245-279 are drawn to a "multimeric complex composition" having "monomeric unit(s)" attached via "polymeric interactions." The language "multimeric complex composition" bound via "polymeric interactions" reads on associations of any polymer, ie. any chemical compound or mixture of compounds combined and consisting of essentially repeating structural units, and therefore reads on nylon or any other non-biological polymeric composition as well as duplex DNA, RNA, etc. The scope of the genus sought for such constructs is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims nebulously claim "multimeric compositions." The specification teaches only prophetically nucleic acid constructs having multimeric units bound to binding matrices for cell interaction. The specification only exemplifies application of constructs for expression of antisense to HIV in which the only "multimeric units" are nucleotides forming duplex DNA "complexes."

Despite the known use in the art of constructs such as nucleic acid vectors having polymeric modifications and conjugated antibodies, etc. for improved cell entry to recombinantly express genes, etc., the broad scope of the instant claims would lead one of ordinary skill in the art to an undue amount of experimentation based on the lack of guidance for making and/or using a representative number of the genus of constructs envisioned by the instant claims as filed.

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Furthermore, the claims specify the context for producing the product in a cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art, for *in vivo* (whole organism) applications. The factors considered are analogous to those in the antisense art for successful delivery of such constructs. The barriers include: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach “although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1).”

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by “raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments.” (Branch, p. 48) Discovery of antisense molecules with “enhanced specificity” *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for

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designing an antisense which inhibits a target *in vivo*: it “is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49).” And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in inhibition of the target, coupled to the amount of “trial and error” experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo*.

No determination of enablement can be made for claims 2-21 because there is no independent claim from which they depend. Without knowing what claims 2-21 depend on, the full scope of the claims is not known.

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6. Claims 2-24 and 245-266 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-21 are drawn to a missing independent claim and therefore the scope claimed is not able to be determined. Claims 22-24 are drawn to a broad scope of constructs which are bound non-ionically to an entity having a chemical modification or a ligand and produce a product in a cell. Claims 245-266 are drawn to a "multimeric complex composition" having "monomeric unit(s)" attached via "polymeric interactions."

The claims broadly encompass "constructs" for producing a "product" and it is not clear what is embraced by the claims. The claims read on vectors, genomes, cell processes like translation, transcription, etc. Furthermore, the scope of "chemical modification" as used in claim 22 is not clear in relation to the construct. Claims 245-266 further read on any polymer composition.

The instant specification describes prophetically a number of potential modified nucleic acid constructs for expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics because they primarily correspond to expression vector based constructs which are only one facet of the invention in light of the nebulous scope claimed.

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Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids. Specifically, for claims 245-266, the only “multimeric compositions” exemplified are those for antisense inhibition of HIV.

Furthermore, the actual constructs used in the HIV challenge and Lac-Z assays taught in the specification are not described in clear and exact terms (p. 169, line 3 recites “U1 clone”; p. 169, para. © line 1 recites “triple U1 construct”; and p. 167, last line recites “various U1 constructs described above”) and it is not clear whether the constructs used had the intron sequence in the T7 polymerase, or even which constructs were used in the assays.

Despite the known predictability of standard vector construction in the molecular biology art, in view of the nearly infinite scope claimed and the lack of adequate description in the specification for such a broad genus of possible “constructs” and “multimeric compositions” coupled with the high level of unpredictability for constructs which could fall within this genus such as those involving gene therapy, the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of “construct” or “multimeric composition” species for the breadth claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C. 112 “Written Description” requirement.

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Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al..

The claimed invention is drawn to any construct which when present in a cell produces a product, and is bound non-ionically to an entity comprising a modification or a ligand, and further comprises a hybridized polynucleotide tail.

Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. Reads on all of the instant claimed limitations for a non-naturally occurring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

9. Claims 245-279 are rejected under 35 U.S.C. 102(e) as being anticipated by Sullivan.

The claimed invention is drawn to any multimeric complex composition bound through polymeric interactions and/or attached to a charged polymer and process of delivery of said multimeric composition to a cell.

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Sullivan teaches compositions and methods for improved cell permeability to negatively charged polymers such as RNA and DNA. Specifically, he teaches application of permeability enhancer molecules and ligand-permeability enhancer molecules containing cationic groups which can ion-pair with anionic groups present on the negatively charged polymer.

10. Claims 245-279 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel et al.

The claimed invention is drawn to any multimeric complex composition bound through polymeric interactions and/or attached to a charged polymer and process of delivery of said multimeric composition to a cell.

Curiel et al. teach conjugates in which a virus is bound via an antibody to a substance having an affinity for nucleic acid, for transporting gene constructs into higher eucaryotic cells and pharmaceutical compositions thereof. It is within the scope of the invention to apply F(ab')₂ fragments and/or complex said antibody with a target comprising an enzyme.

11. Claims 245-266 and 275 are rejected under 35 U.S.C. 102(e) as being anticipated by Edwards et al.

The claimed invention is drawn to any multimeric complex composition bound through polymeric interactions and/or attached to a charged polymer.

Edwards et al. teach the design of sequence-specific DNA-binding drugs (and methods of detecting) comprised of homo- or hetero-meric subunits of molecules and the use of said molecules as covalently attached moieties to aid in the binding of nucleic acid or other macromolecular polymers to nucleic acid sequences.

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12. Claims 245 and 275-279 are rejected under 35 U.S.C. 102(e) as being anticipated by Buechler et al.

The claimed invention is drawn to any multimeric complex composition bound through polymeric interactions and/or attached to a charged polymer. Specifically in claims 276-279, multimeric compositions comprising protein and/or antibody components.

Buechler et al. teach complexes of ligand-receptor and target-ligands.

13. Claims 245-279 are rejected under 35 U.S.C. 102(e) as being anticipated by Paul et al.

The claimed invention is drawn to any multimeric complex composition bound through polymeric interactions and/or attached to a charged polymer and process of delivery of said multimeric composition to a cell.

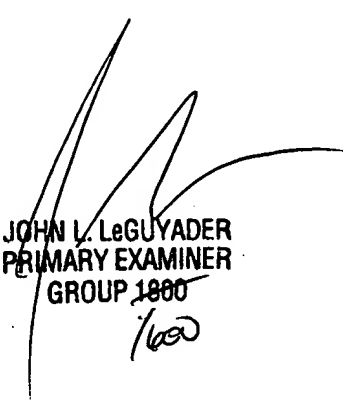
Paul et al. teach retroviral vectors for directing gene delivery to a specific sub-population of mammalian cells. The vectors having chimeric targeting proteins containing a ligand moiety capable of binding to receptors present on target cells and an uptake moiety promoting entry of the vector into the target cell.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.


JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1800
1/6/00